To:	**Food & Drug Administration – Food Advisory Committee**
From:	**Nutramax Laboratories, Inc. – Edgewood, Maryland**
Date:	**May 28, 2004**
Re:	**Written Comments at Public Meeting – June 7 & 8, 2004** **Health Claim Petition: Glucosamine Sulfate & Osteoarthritis filed by Rotta Pharmaceuticals, Inc. Docket No. 2004P-0060**

We appreciate the opportunity to submit these written comments to the Food & Drug Administration Food Advisory Committee for the above referenced public meeting and health claim petition.

There are several issues in this health claim petition regarding assay methods and claims on effectiveness that should be considered very thoroughly.

1. The National Institutes of Health is conducting a large clinical study, the Glucosamine/Chondroitin Sulfate Arthritis Intervention Trial (GAIT)[1], using glucosamine hydrochloride and chondroitin sulfate, not glucosamine sulfate. The rationale for this approach is based on the assumption that glucosamine alone produces the observed clinical effects observed in studies of glucosamine. Furthermore, recent clinical studies on glucosamine sulfate that lacked active industry involvement in analysis and description of data have not found the benefit previously observed in studies supported by Rotta[2-6]. Further research is clearly needed with better endpoints to eliminate bias and resolve these differences.

2. The petitioner's argument that the sulfate component of glucosamine sulfate plays a significant role in its biological effects is at best only speculative. Biochemical studies show that glucosamine hydrochloride alone produces effects on chondrocytes that may underlie the ameliorative effects of this supplement[7-12]. The petitioner's distinction between the clinical effects of glucosamine hydrochloride and glucosamine sulfate is questionable based on the available independent research on bioavailability and effectiveness of glucosamine base. Many experts feel that the base is active irrespective of salt.

3. The petitioner claims to have a validated assay for glucosamine sulfate that is specific, accurate and precise, and that is based on a potentiometric measurement. Examination of the attachment in the health claim petition describing this method indicates no data showing specificity for glucosamine sulfate. Many organic molecules with a primary amine group will give the same result as glucosamine when titrated as described, as such it is by definition not specific. In fact, the method relies on the use of a factor to correct for the endpoint in the titration that is present due to an excipient, citric acid. An alternative, specific, commonly used

assay must be used in analyzing the petitioner's glucosamine sulfate to ascertain what is actually present and being studied clinically.

4. At present there are several methods available that can be used to analyze glucosamine and glucosamine sulfate, but many suffer limitations. The petitioner criticizes the USP method while at the same time offering it as an indicator of the exact composition of glucosamine sulfate for which a claim is sought. Part of the criticism of the indicated USP method may be justified (use of detection wavelength that is relatively nonspecific), but the evidence provided regarding chloride detection is questionable. When properly run, the HPLC procedure will result in elution of glucosamine at a specific retention time that does not coincide with chloride. There is a clear need for clarification and uniformity in the industry in analysis methodology prior to granting any type of health claim for glucosamine sulfate.

5. The petitioner asks for a health claim on "crystalline glucosamine sulfate" with the implicit assumption that the specific glucosamine sulfate being considered is the same as the form for which petitioner has a patent that relates to its method of preparation. The term "crystalline glucosamine sulfate" should be clearly defined. Were the studies cited performed on this patented formulation and is it strictly this formulation for which the health claim is requested? The USP clearly states that "practically all the glucosamine products available in the current market is the mixed salt or co-crystals of glucosamine hydrochloride with sodium or potassium sulfate"[11]. At different times the USP has used two different formulas to represent glucosamine sulfate containing sodium:

   $(C_6H_{13}NO_5 \cdot HCl)_2 \cdot Na_2SO_4$ and $(C_6H_{14}NO_5)_2SO_4 \cdot 2NaCl$

   The molar ratio of glucosamine:sulfate:sodium:chloride is 2:1:2:2 for both. These formulas may be intended to reflect the method of production of "glucosamine sulfate". While the crystalline products are indistinguishable upon dissolution they may differ in their stabilities as crystals. In contrast, glucosamine hydrochloride does not suffer from this ambiguity and is highly stable.

6. Recent studies of the contents of glucosamine in various commercial products, particularly glucosamine sulfate, showed levels substantially less than that claimed on the labels[14,15]. This situation reinforces the importance of consistent methodology and accuracy, or truth, in labeling.

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